## REMARKS

The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Applicants have cancelled 6 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 1 to remove reference to the Figure and to recite that the claimed antibody specifically binds to the polypeptide of SEQ ID NO: 74.

Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed August 3, 2004. For the reasons set forth below, Applicants respectfully traverse.

**Correction of Inventorship under 37 CFR §1.48(b)**

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

**Priority Determination**

Applicants acknowledge that the PTO has granted the present application the priority date of **August 24, 2000**. Applicants note that SEQ ID NO: 74 was first disclosed as SEQ ID NO: 2 in U.S. Provisional Application 60/099763, filed September 10, 1998.

**Specification**

The disclosure was objected to by the PTO as containing trademarks which were not capitalized and did not include the generic terminology. The specification has been amended to include these changes. The specification has been further amended to remove reference to embedded hyperlinks.

**Rejection under 35 U.S.C. §101 – Utility**

The PTO has rejected Claims 1-6 as lacking a specific and substantial, or well-established utility. The PTO argues that the polypeptide of SEQ ID NO: 74 has no utility. The PTO argues that uses such as assaying for binding partners, using polypeptides as molecular weight markers, and screening for agonists and antagonists of PRO1335 are useful only in research to determine the function of the encoded protein itself. The PTO also states that the specification does not disclose any disease or conditions known to be associated with the encoded protein, and therefore modified antibodies to the PRO1335 polypeptide cannot be used to treat cancer or HIV. Finally, the PTO states that the invention lacks a well-established utility.

Applicants respectfully disagree that they have not established a substantial and specific utility for the claimed antibodies.

*Utility – Legal Standard*

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

*Utility – Evidentiary Standard*

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

**Substantial Utility**

*Applicants have established that the Gene Encoding the PRO1335 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool*

For the reasons stated below, Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the disclosed polypeptides and antibodies as diagnostic tools for cancer, as described in the specification, for example, at paragraph [0407].

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). As Mr. Grimaldi states, "If a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (Paragraph 7, emphasis added).

The data presented in Example 18 show that the gene encoding PRO1335 is more highly expressed in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. As the Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools. No additional research into how PRO1335 is related to cancer is required to use the disclosed polynucleotides, polypeptides and antibodies to distinguish tumor cells from their normal tissue counterparts. This establishes a substantial utility for the claimed antibodies.

*Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein*

The PTO also states that the specification does not disclose any disease or conditions known to be associated with the encoded protein. Applicants respectfully disagree.

The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO1335 in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. Applicants assert that it is well-established in the art that the level of protein is positively correlated to the level of mRNA. Therefore, one of skill in the art would recognize that the PRO1335 protein is most likely more highly expressed in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma

tumor, respectively. This conclusion is supported by the declarations and references discussed below.

As stated above, the standard for utility is not absolute certainty, but rather *whether one of skill in the art would be more likely than not to believe the asserted utility.* The working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1335 mRNA is expressed

at a higher levels in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively, the PRO1335 polypeptide will also be expressed at higher levels in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. One of skill in the art would recognize that a gene and its encoded a protein which are differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as diagnostic tools, as would antibodies to the protein. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed antibodies.

*The Claimed Antibodies would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression*

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1335, which Applicants submit is not true, antibodies to a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 4), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 5). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu

gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, antibodies to a protein encoded by a gene that is differentially expressed in cancer would still have utility as a diagnostic tool. Thus, Applicants have demonstrated another basis of support for the utility of the claimed antibodies.

**Specific Utility**

*The Asserted Substantial Utilities are Specific to the Claimed Antibodies*

Applicants next address the PTO's assertion that the claimed antibodies lack a specific utility. Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1335 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene encoding the PRO1335 polypeptide is more highly expressed in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. It is well-established in the art that the encoded protein would have the same expression pattern. These data are therefore strong evidence that the PRO1335 polypeptide is associated with stomach, lung, rectal, and melanoma tumors. This is a specific utility – it is not a general utility that would apply to the broad class of polypeptides or antibodies. Thus, contrary to the assertions of the PTO, Applicants submit that they have established that the asserted utilities are specific to the claimed antibodies.

**Conclusion**

The PTO has asserted that the claimed invention lacks a substantial and specific utility. Applicants submit that they have established that the claimed antibodies have both a substantial and a specific utility.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1335 gene in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively, are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed nucleic acids and associated polypeptides and antibodies have utility as cancer diagnostic tools.

Next, Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that antibodies to the PRO1335 proteins have utility as diagnostic tools for cancer, further supporting the asserted utility.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, antibodies to a protein encoded by a gene differentially expressed in cancer is useful as a diagnostic tool.

Finally, the PTO asserts that there is no asserted specific utility for the claimed antibodies. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the gene encoding PRO1335, and presumably the PRO1335 polypeptide, are differentially expressed in certain cancer cells compared to the corresponding normal cells. The utility of a diagnostic tool for cancer is not a general utility that would apply to the broad class of antibodies, since not all antibodies bind to polypeptides that are differentially expressed in cancer.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is <u>not</u> required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the asserted utility for the disclosed nucleic acids, polypeptides, and antibodies relating to PRO1335. In view of the above, Applicants respectfully request that the PTO withdraw the utility rejection under 35 U.S.C. §101.

**Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness**

The PTO has rejected Claim 6 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "specifically binds", stating that it is a relative term that renders the claim indefinite. The PTO argues that specifically is not defined in the claims and the specification does not provide a standard for ascertaining the requisite degree of binding.

Claim 6 has been cancelled and Claim 1 amended to recite "specifically binds". Applicants submit that the term "specifically binds" has a well established meaning – it refers to the binding of an antibody to a particular polypeptide, where the antibody does not substantially bind to any other polypeptide. One of skill in the art would readily understand the language of the claims to mean that the claimed antibodies bind to specifically defined polypeptides (in this case the polypeptides of SEQ ID NO: 74) but do not substantially bind to any other polypeptides. Since claim terms should be given their ordinary, art-recognized meaning, Applicants submit the present rejection is misplaced, and request that it be withdrawn.

**Rejection under 35 U.S.C. §112, first paragraph – Enablement**

The PTO rejected Claims 1-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, and specific utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

**Rejection under 35 U.S.C. §103(a) – Obviousness**

The PTO rejects Claims 1-6 under 35 U.S.C. § 103(a) as unpatentable over Fujikawa-Adachi *et al.* (Genomics, 61:74-81 (1999)). The PTO asserts that Fujikawa-Adachi *et al.* disclose a polypeptide that is 100% identical to SEQ ID NO: 74. However, the PTO states that Fujikawa-Adachi *et al.* do not teach antibodies that bind to the polypeptide. The PTO asserts that it would have been obvious to a person of ordinary skill in the art to make such antibodies because it is a commonly employed laboratory technique, citing U.S. Patent Nos. 6,024,955;

6,008,325; or 5,994,088 as examples. The PTO concludes that the invention is therefore obvious in light of the prior art.

Applicants submit that they are entitled to priority to U.S. Provisional Application No. 60/099763, filed September 10, 1998. This Provisional Application discloses the full length sequence of SEQ ID NO: 74. Applicants also submit herewith a copy of a Declaration of the co-inventors under 37 C.F.R. § 1.131 (attached as Exhibit 6), originally filed in the related co-pending and co-owned application, Serial No. 10/063,709, which establishes that the presently claimed invention antedates the Fujikawa-Adachi *et al.* reference. The declaration and the supporting evidence submitted therewith establish conception of the invention prior to September 10, 1998, well before the October 1, 1999 publication date of the Fujikawa-Adachi reference, and diligent reduction to practice of the invention thereafter. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §103(a) be withdrawn.

## CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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